Via EFS
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Attorney Docket No. 35147-503N01US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Roberto Pellicciari		
Serial Number:	10/590,848	Examiner:	Barbara P. Badlo
Filing Date:	July 3, 2007	Art Unit:	1612
For:	Novel Steroid Agonist for FXR		

DECLARATION OF DR. ROBERTO PELLICCIARI PURSUANT TO 37 C.F.R. § 1.132

I, the undersigned Roberto Pellicciari, hereby declare and state that:

1. I am Dr. Roberto Pellicciari, Ph.D., Head of Medicinal Chemistry at Intercept Pharmaceuticals, Inc. (referred to herein as "Intercept"). I am also a Professor of Medicinal Chemistry at the Department of Chemistry and Technology of Drugs of the University of Perugia (Italy) and Adjunct Professor at MPRC-School of Medicine, University of Maryland, (USA). I received my Doctorate Degree with a thesis in the Istituto Superiore di Sanità in Rome and have spent more than twenty-five years involved in the fields of medicinal chemistry and bile acid research. I have also been President of the Division of Medicinal Chemistry of the Italian Chemical Society (2001-2003) and President of the European Federation of Medicinal Chemistry (EFMC) (2006-2008). I have authored or co-authored more than 330 scientific publications and am the named inventor on about 25 issued or pending patents.

2. I am aware of the Office Action dated August 20, 2009 in the above-identified application (referred to herein as the "Application"). I understand that the claimed compound in the Application has been rejected as being obvious over the compounds in European Patent No. 312,867 to Frigerio ("Frigerio").

3. I have reviewed the available data comparing the claimed compound in the Application with the compounds disclosed in Frigerio.

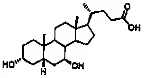
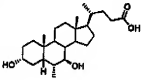
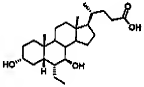
4. It is my opinion that the claimed invention is not obvious in view of Frigerio, at the least because of surprising, unexpected and improved properties that have been found for the present invention.

5. The Office Action alleges that, in view of the 6-methyl UDCA derivatives disclosed in Frigerio, the claimed compound 6-alpha-ethyl UCDA is obvious. Specifically, the Office Action states that it would be obvious for a person skilled in the art to make the 6-ethyl substituted UDCA derivative based on the teachings in Frigerio and the level of skill of the ordinary artisan in the art at the time of the present invention. As I understand it, the Office Action states that the 6-methyl derivative of UDCA is an adjacent lower homolog of the claimed compound, the 6-ethyl UDCA derivative, and that the present invention would have been obvious because the skilled artisan would have expected the two compounds to have similar properties.

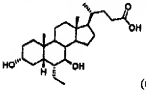
6. However, modification of chemical structures is an unpredictable art and for any particular chemical modification one skilled in the art would not be able to predict differences in biological activity including such properties as potency.

7. The Farnesoid X Receptor (FXR), discovered in 1999, is a receptor for bile acids. Researchers at GlaxoSmithKline have conducted experiments comparing the activity of UDCA and certain 6-methyl and 6-ethyl substituted UDCA derivatives on the FXR receptor as shown in Table 1. FXR activity was determined using an in vitro assay measuring the recruitment of the FXR co-activator SRC1.

Table 1.

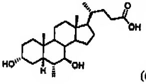
Compound	Chemical Structure	FXR EC_{50}	FXR efficacy
UDCA		>50 µM	4.7%
6-alpha Me UDCA		34.49 µM	66%
6-alpha Et UDCA		4.58 µM	85%

8. Research scientists at GlaxoSmithKline have conducted experiments comparing FXR activity of the claimed compound 6-EtUDCA:

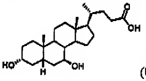


(6-EtUDCA)

with the FXR activity of 6-MeUDCA and the parent compound UDCA:



(6-MeUDCA)



(UDCA).

9. For FXR agonists which are candidates for the treatment of an FXR mediated disease or condition such as hypercholesteremia, hyperlipidemia, low HDL-cholesterol, and high triglycerides, FXR activity is an important criteria.

10. The FXR activity of the claimed compound, 6-EtUDCA as compared to UDCA and 6-MeUDCA using a standard cell-based FXR activity assay was found to be dramatically and unexpectedly different.

11. In the assay, the results of which are shown in Table 1, the ability to bind FXR was tested. The SRC1 peptide is recruited in the presence of ligands to the receptor. The amount of binding was measured by Fluorescence Resonance Energy Transfer (FRET). The results show that the EC_{50} of the claimed compound, 6-alpha ethyl UDCA was 4.58 μM, whereas the EC50 of the 6-alpha methyl UDCA is 34.49 μM. This significant increase in potency for the claimed compound is unexpected and highly desirable as it likely to produce a more efficacious, active compound with fewer unwanted side effects.

12. I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. § 1001 and that willful false statements may jeopardize the validity of this application and any patent issuing therefrom.

Dr. Roberto Pellicciari

Signed this 22 day of February 2010